Phosphite-Reduction of Aromatic Nitro-Compounds as a Route to Heterocycles

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This review deals with the ring closure reactions which occur on reduction of appropriate aromatic nitro compounds and which, in many cases, represent a useful synthetic pathway to nitrogen-containing heterocycles.

Tervalent phosphorus compounds (X_3P), such as trialkyl or triarylphosphines and trialkyl phosphites react with a wide variety of oxygen-containing compounds to yield the corresponding quinquevalent derivatives (X_3PO)[1]:

$$X_3P + ZO \longrightarrow X_3PO + Z$$

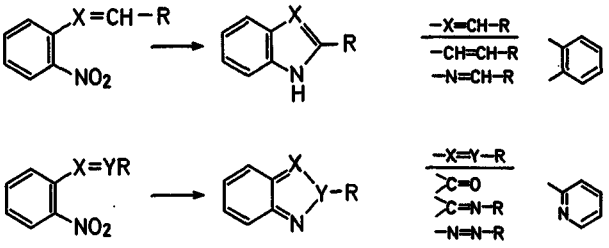
Many examples of this general reaction have been known for some time[1], but those involving reduction of aromatic nitro- and nitroso-compounds have received widespread attention during the last few years only. Since the discovery[2] of the reaction in 1962, the reduction of nitro-compounds by triethyl phosphite and related reagents has been recognised as a general route to a wide variety of nitrogen-containing heterocyclic compounds, including carbazoles[2,3,4], carbolines[5], indoles[2,3,6] indazoles[3], benzotriazoles[3], anthranils[7], phenothiazines[8], 3H-azepines[9], benzoxazoles, and related compounds.
This review is directed towards the scope of this reaction. A more comprehensive review, involving a discussion of mechanistic factors, is available[10].

Summary of the General Reaction.

In general, the nitro-compound is allowed to reflux under nitrogen, in a solvent, e.g. t-butylbenzene, either with two equivalents of the tervalent phosphorus reagent (usually triethyl phosphite) or, more usually, in an excess of the phosphite:

$$Ar{-}NO_2 + 2(C_2H_5O)_3P \longrightarrow 2(C_2H_5O)_3PO + Ar{-}N\!:$$

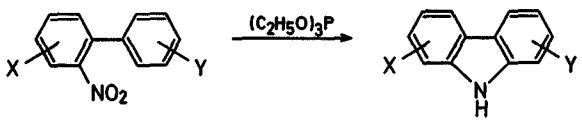
There is strong evidence[10] that the reaction proceeds via the intermediacy of a nitrene which, if generated in proximity to a suitable side chain reacts to give a five-membered nitrogen-containing heterocycle or intermediate. Such a reaction usually involves insertion into aliphatic or aromatic C-H bonds or combination with electronegative atoms such as nitrogen or oxygen:



1. Synthesis of Five-Membered Nitrogen-Containing Heterocycles

1.1 Carbazoles, Carbolines and Benzocarbazoles

Carbazoles are formed from the corresponding 2-nitrobiaryl in moderate to excellent yields (35–83%):



X,X′ = H, Br, CH_3, Cl or polymethyl[11]

Carbazole[3]: A mixture of 2-nitrobiphenyl (3.98 g; 0,02 mol) and triethyl phosphite (13.28 g; 0,08 mol) is allowed to reflux under nitrogen for 9 hr. Subsequent distillation of the red solution gives triethyl phosphite (6.7 g), b. p. 41°/0.2 mm, and triethyl phosphate (6.66 g), b. p. 51°/0.2 mm. The solid residue is treated with hot acetone, the solution evaporated, (the resulting pale yellow solid stirred with light petroleum (b. p. 60—80°) and filtered to give carbazole as a colourless solid; yield: 2.77 g (83%); m. p. 247—248°.

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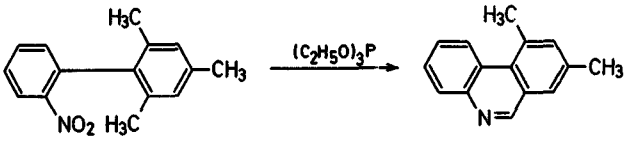
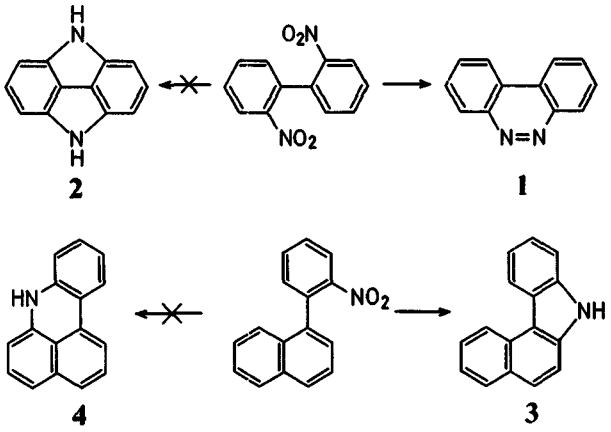
[1] J. I. G. CADOGAN, Quart. Reviews, **16**, 208 (1962).
[2] J. I. G. CADOGAN and M. CAMERON-WOOD, Proc. Chem. Soc. **1962**, 361.
[3] J. I. G. CADOGAN, M. CAMERON-WOOD, R. K. MACKIE, and R. J. G. SEARLE, J. Chem. Soc., **1965**, 4831.
see also J. I. G. CADOGAN and R. K. MACKIE, Org. Synth., **48**, 113 (1968).
[4] I. PUSKAS and E. K. FIELDS, J. Org. Chem., **33**, 4237 (1968).
[5] T. KAMETAMI, T. YAMANAKA, and K. OGASAWARA, Chem. Commun., **1968**, 996.
[6] R. J. SUNDBERG and T. YAMAZAKI, J. Org. Chem., **32**, 290 (1967).
[7] J. I. G. CADOGAN, R. K. MACKIE, and M. J. TODD, Chem. Commun., **1966**, 491.
[8] J. I. G. CADOGAN, S. KULIK, and M. J. TODD, Chem. Commun., **1968**, 736.
[9] J. I. G. GADOGAN and M. J. TODD, Chem. Commun., **1968**, 178.
[10] J. I. G. CADOGAN, Quart. Reviews, **22**, 222 (1968).
[11] I. PUSKAS and E. K. FIELDS, J. Org. Chem., **33**, 4237 (1968).
[12] P. J. BUNYAN and J. I. G. CADOGAN, J. Chem. Soc., **1963**, 42.
[13] T. KAMETANI, K. OGASAWARA, and T. YAMANAKA, J. Chem. Soc. [C], **1968**, 1006.

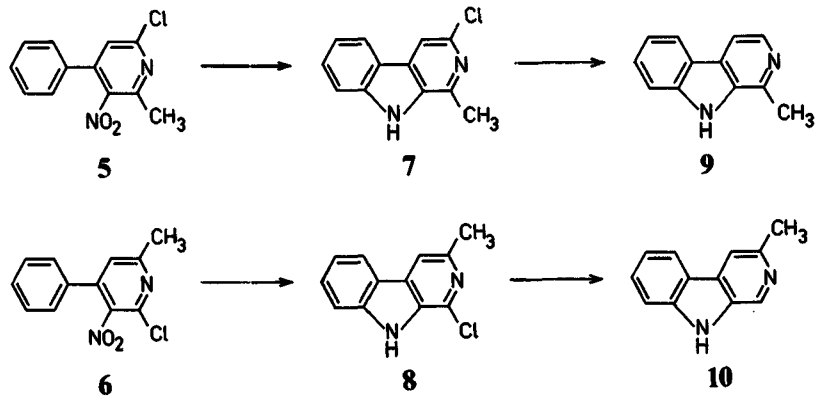
Other reactions occur when both ortho-positions are blocked. For instance, 2-nitro-2',4',6'-trimethylbiphenyl gives 8,10-dimethylphenanthridine (14%) among other products, when the reaction is carried out in an inert solvent[9]:



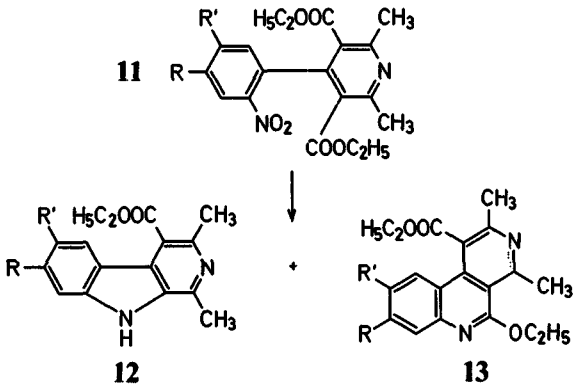
The reaction of 2,2-dinitrobiphenyl affords only a low yield (1,5%) of benzo[c]cinnoline (**1**) rather than the possible alternative **2**,[3] while 1-(2-nitrophenyl)-naphthalene is reduced to 7H-benzo[c]carbazole (**3**) rather than the isomeric six-membered heterocycle **4**:



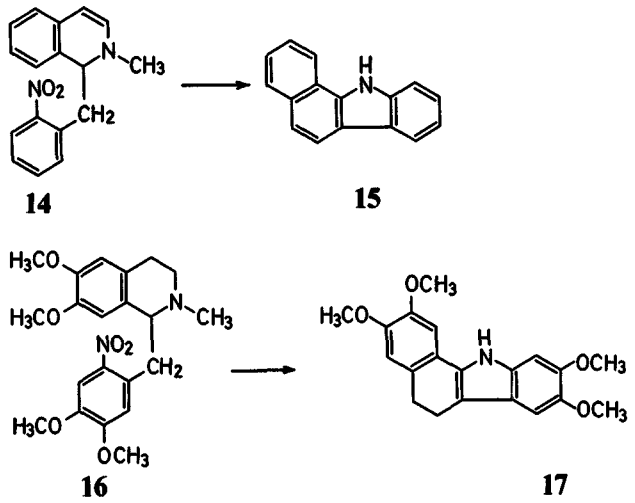
In analogy to the reductive cyclization of nitrosophenyl-pyridines to carbolines by triethyl phosphite[12], nitrophenylpyridines have been converted to carbolines. Thus, the reaction of 6-chloro-3-nitro-2-methyl-4-phenylpyridine (**5**) and 2-chloro-3-nitro-6-methyl-4-phenylpyridine (**6**) with triethyl phosphite affords the corresponding chloro-methyl-β-carbolines (**7**, **8**), which upon dechlorination give 1-methyl-β-carboline (harman, **9**) and 3-methyl-β-carboline (**10**), respectively[13]:



The 4-(2-nitrophenyl)-pyridine **11**, upon reaction with triethyl phosphite, gives the β-carboline **12** (20%) indicating nitrene insertion into a C—C-bond, together with the benzo[c]naphthyridine **13** (24%) indicating insertion into the C=O-double bond of the ethoxycarbonyl group:



Rearrangement occurs on reaction of triethyl phosphite with 2-methyl-1-(2-nitrobenzyl)-1,2-dihydroisoquinoline (**14**) or 6,7-dimethoxy-2-methyl-1-(2-nitro-4,5-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (6-nitro-laudanosine, **16**) to give benzo[a]carbazole (**15**) and the corresponding tetramethoxydihydro derivative (**17**), respectively[15]:



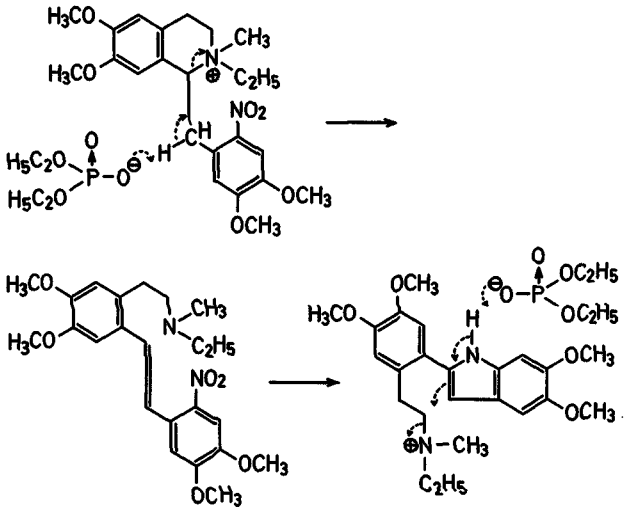
[14] T. KAMETANI, T. YAMANAKA, and K. OGASAWARA, J. Chem. Soc. [C], **1969**, 138.

[15] T. KAMETANI, T. OGASAWARA, and T. YAMANAKA, J. Org. Chem., **33**, 4446 (1968).

[16] J. I. G. CADOGAN and M. J. TODD, unpublished.

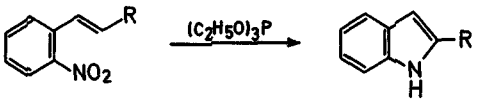
[17] E. E. TAYLOR and E. C. GARCIA, J. Org. Chem., **30**, 655 (1965).

The mechanism of this interesting reaction has not been established but the failure of cyclization in the case of the corresponding methiodides leads the reviewer to suggest the following scheme:



1.2. Indoles and Related Compounds

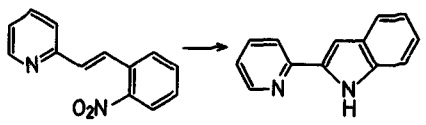
The reaction of triethyl phosphite with *cis*- and *trans*-2-nitrostilbene and α-nitrostilbene affords 2-phenylindole (**18**) in 85, 58, and 16% yields, respectively[5]:



18

Under these conditions, α-(2-nitrophenyl)-β-(2-chlorophenyl)-acrylic acid gives 2-(2-chlorophenyl)-3-ethoxycarbonylindole[16] (46%), indicating the occurence of esterification, presumably by triethyl phosphate, during the reaction.

The reductive cyclization of 2-(2-nitrostyryl)-pyridine which presents two possible points of ring closure, also gives rise to an indole (**19**) rather than proceeding via reaction at the electron-rich nitrogen to give a diazepine[16]:



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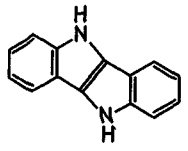
Under similar conditions, 2-nitrostyrene and 2,2'-dinitrostilbene give small yields (1—2%) only of indole and indolo-[3,2-b]-indole (**20**),



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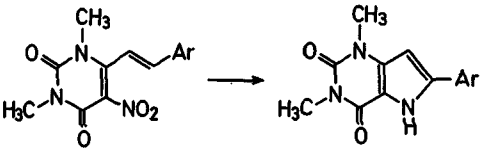
[18] R. J. SUNDBERG, J. Org. Chem., **30**, 3604 (1965); J. Amer. Chem. Soc., **88**, 3781 (1966).

[19] R. J. SUNDBERG and T. YAMAZAKI, J. Org. Chem., **32**, 290 (1967).

respectively, while the reaction of ω-nitrostyrene gives no indole, and 2-nitrocinnamic acid is reduced and esterified to give a low yield of indole-2-carboxylic acid ester[3].

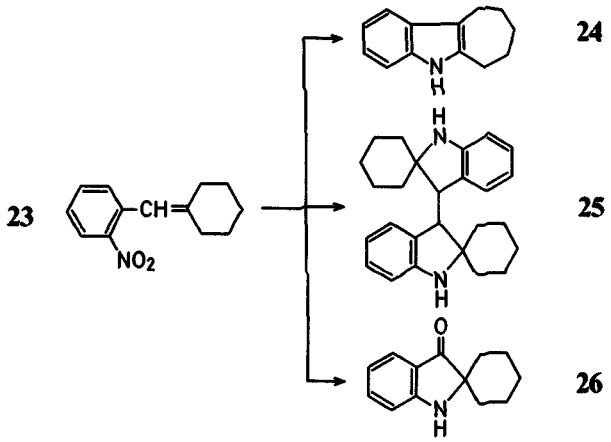
Two of the biologically interesting pyrrolo[3,2-d]pyrimidines **22** have been prepared, in low yield, from the corresponding 5-nitro-6-styrylpyrimidine derivatives **21**, thermally and by u.v. irradiation in the presence of triethyl phosphite:



21 **22**

In the latter case, however, some warming occured, so that the products may be arising by a thermal process. The indole synthesis has been extended[18] to include 2-alkyl(CH_3; C_2H_5; 50—60% yields) and 2-acyl(CH_3CO; C_6H_5CO; 16% yields)-indoles. Minor by-products of mechanistic interest are also formed.

In the corresponding reaction of β,β-disubstituted 2-nitro-styrenes[19], indoles are again the major products. Thus, cyclohexylidene-(2-nitrophenyl)-methane (**23**) undergoes ring closure with rearrangement to give 5,6,7,8,9,10-hexahydro-cyclohepta[b]indole (**24**; 35%) together with lower yields of the bi-indolyl **25** (24%) and the spiro-indolinone **26** (8%) shown in the following scheme:

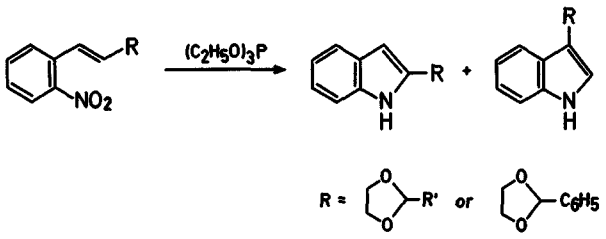


24 **25** **26**

Similarly, the reaction of 2-nitro-β,β-dimethylstyrene with triethyl phosphite gives 2,3-dimethylindole (33%), while that of 2-phenyl-1-(2-nitrophenyl)-propene (2-nitro-α-methylstilbene) gives a high yield (77%) of the rearranged indole, 2-methyl-3-phenylindole, together with the N-ethyl derivative (21%) formed by alkylation of the first formed indole by triethyl phosphate. A further extension of the indole

[20] R. J. SUNDBERG, J. Org. Chem., **33**, 487 (1968).

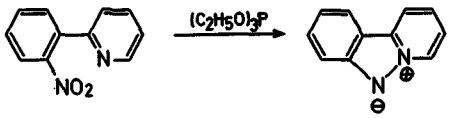
synthesis involving migration of a β-substituent in a mono-substituted 2-nitrostyrene is outlined in the *following scheme*[20]:



Low yields (< 20%) of indolines can also be prepared by the corresponding reaction of 2-nitro-alkylbenzenes (alkyl > C_2H_5)[18].

1.3. Indazoles, Triazoles, Imidazoles, Tetraazapentalenes, and Related Polycyclic Derivatives

Reduction of 2-(2-nitrophenyl)-pyridine (**27**) leads to cyclisation at nitrogen to afford pyrido[1,2-b]indazole (**28**) in almost quantitative yield[3]:



27 **28**

This reaction opened the way to successful cyclisations of N-(2-nitrobenzylidene)-anilines to 2-arylindazoles[3] (**29**):

29

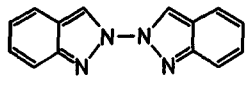
Ar = C_6H_5, o—C_6H_4—Br, p—C_6H_4—OCH_3, p—C_6H_4—CH_3, o—C_6H_4—CH_3, naphthyl-1; yields: 35—38%.

and of 2-nitro-azoarenes to the corresponding benzotriazoles[3] (**30**), except in the case of 2-nitro-4′-hydroxyazobenzene which undergoes ethylation as well as reductive cyclisation to give 2-(4-ethoxyphenyl)-2H-benzotriazole:

30

Ar = C_6H_5, p—C_6H_4—Br, p—C_6H_4—OCH_3, p—C_6H_4—Cl, p—C_6H_4—CH_3; yields: 31—37%.

Similarly, the reaction of 2-nitrobenzaldazine yields 2,2′-bi-2H-indazolyl (**31**) and that of bis-[2-nitrobenzylidene]-p-phenylenediamine yields 1,4-bis-[2H-indazolyl-2]-benzene (**32**),



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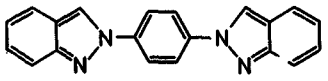

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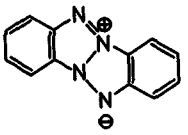
while the five-membered ring system, dibenzo[b;f]-1,3a,4,6a-tetraazapentalene (**33**) is readily obtained from 2,2′-dinitro-azobenzene[3]:



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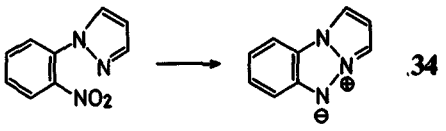
Extensions of these reactions include the formation of *pyrazolo[1,2-a]benzotriazole* (**34**; 18%) from 1-(2-nitrophenyl)-pyrazole[21]



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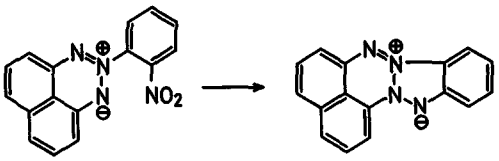
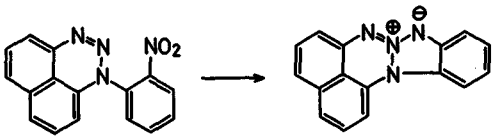
and of benzotriazolo[2,1-a]-naphtho[1,8-d,e]triazine (**36**; 46%)[22] from the naphthotriazine **35**:



35 **36**

Similarly is formed the isomeric benzotriazolo[1,2-a]-naphtho[1,8-d,e]-triazine **37** from the corresponding triazine[23]



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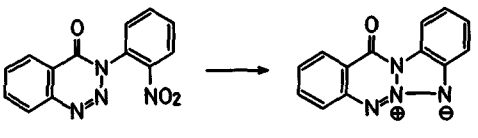
and 13-oxo-⟨benzotriazolo[2,1-b]-benzo[e]-triazine⟩ (**38**) from 4-oxo-3,4-dihydro-benzo-1,2,3-triazine[24]:



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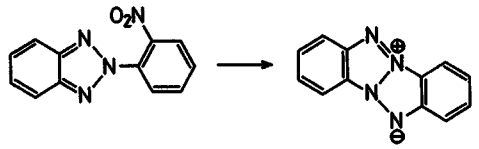
[21] Y. Y. Hung and B. M. Lynch, J. Heterocyclic Chem., **2**, 218 (1965).

[22] H. Sieper, Tetrahedron Letters, **1967**, 1987.

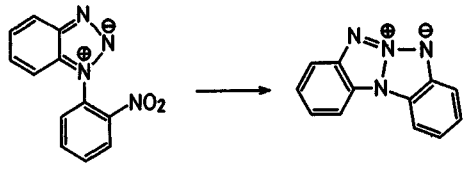
[23] H. Sieper and P. Tavs, Ann. Chem., **704**, 161 (1967).

[24] A. W. Murray and K. Vaughn, Chem. Commun., **1967**, 1283.

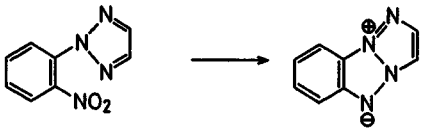
Similarly, 2-(2-nitrophenyl)-2H-benzotriazole (**39**), 1-(2-nitrophenyl)-1H-benzotriazole (**41**), and 2-(2-nitrophenyl)-1,2,3-triazole (**43**) are readily converted (61—88% yield)[25] into the mono- and dibenzo-tetra-azapentalenes **40**, **42**, and **44**:



39 **40**

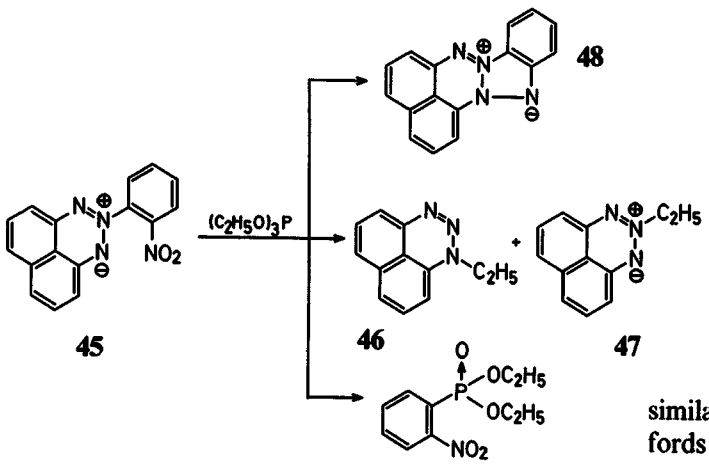


41 **42**



43 **44**

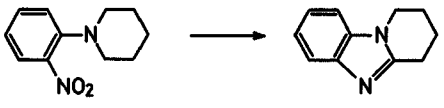
Treatment of 2-(2-nitrophenyl)-2H-naphtho[1,8-d,e]-1,2,3-triazine (**45**) with triethyl phosphite affords[26] diethyl *2*-nitrobenzenephosphonate and the ethylated triazines **46** and **47** in addition to the expected tetra azapentalene **48**:



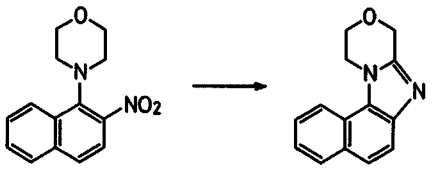
45 **46** **47** **48**

Diethyl 2-nitrobenzenephosphonate is also produced as a side product in the reaction of triethyl phosphite with 4-oxo-3,4-dihydro-benzo-1,2,3-triazine[24], thus recalling the substitution of 1,2-dinitrobenzene with trivalent phosphorous reagents[27].

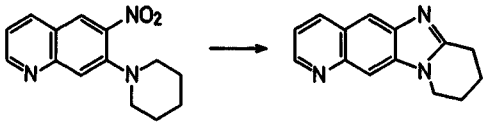
Reductive cyclisation of the nitro derivatives **49**, **51**, **53**, and **55** with boiling triethyl phosphite gives the corresponding imidazoles **50**, **52**, **54**, and **56** in 23—77% yield[28];



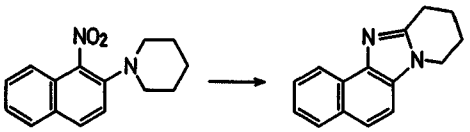
49 **50**



51 **52**

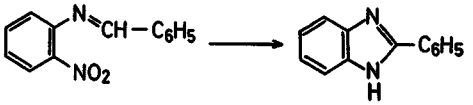


53 **54**



55 **56**

similar treatment of benzylidene 2-nitroanaline affords the parent benzimidazole[29] **57**:



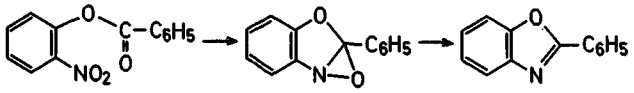
57

1.4. Benzoxazoles, Anthranils, and Furoxans

Reductive cyclisation of 2-nitrophenyl benzoate with excess of triethyl phosphite in t-butyl benzene gives[30]

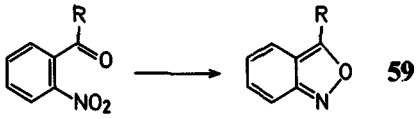
[25] J. C. KAUER, and R. A. CARBONI, J. Amer. Chem. Soc., **89**, 2633 (1967).
[26] H. SIEPER, Tetrahedron Letters, **1967**, 1987.
[27] J. I. G. CADOGAN, D. J. SEARS, and D. M. SMITH, Chem. Commun., **1966**, 491.
[28] H. SUSCHITZKY and M. E. SUTTON, J. Chem. Soc. [C], **1968**, 3058.
[29] J. I. G. CADOGAN, R. MARSHALL, and D. M. SMITH, unpublished.
[30] D. SAUNDERS, Chem. Commun., **1969**, in press.

2-phenyl-benzo-1,3-oxazole (**58**; 60%) presumably via nitrene insertion into the C=O group followed by deoxygenation:



58

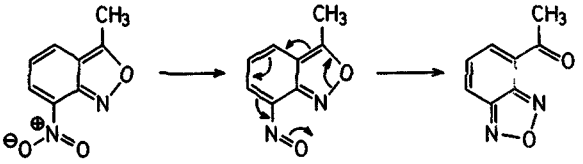
Benzo[c]-1,2-oxazoles (anthranils, **59**) are similarly obtained from 2-nitrophenylketones[7]:



59

Thus, the reaction of 2-nitrobenzophenone with triethyl phosphite gives 3-phenyl-benzo[c]-1,2-oxazole (56%) and 2-aminobenzophenone (19%), the latter product suggesting the intermediacy of a nitrene; the reaction of 2-nitrochalcone and 5-chloro-2-nitroacetophenone affords no cyclised product, the only product isolated being diethyl N-(2-acetylphenyl)-phosphoramidate (10%), the presence of which suggests the intermediacy of the corresponding phosphorimidate and hence a nitrene. Although possible extension of this synthesis of benzo[c]-1,2-oxazoles (anthranils) has not received a great deal of attention there is some evidence that it is not of wide applicability[31].

The conversion of 7-nitro-3-methyl-benzo[c]-1,2-oxazole (**60**) into 4-acetyl-benzofuroxan (**61**) under the influence of triethyl phosphite has been effected[32]:

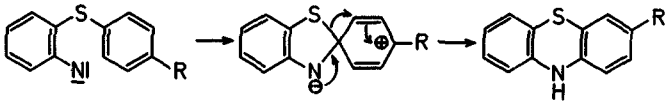


60 **61**

2. Six-membered Nitrogen containing Heterocycles

2.1. Phenothiazines

Phenothiazines (**62**; ~60%) are formed by reductive cyclisation of 2-nitroaryl aryl sulphides; the reaction probably proceeds via rearrangement of a first formed five membered intermediate[8]:



62

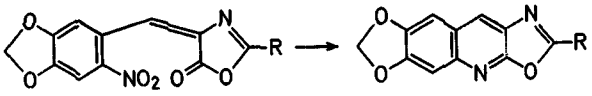
Thus, while (4-methyl-2-nitrophenyl)-phenyl sulphide gives the expected 2-methylphenothiazine, the isomeric 4-methylphenyl 2-nitrophenyl sulphide affords 3-methylphenothiazine.

3-Chlorophenothiazine (**62**, R = Cl): 4-Chlorophenyl 2-nitrophenyl sulfide (2 g; 0.009 mol) and triethyl phosphite (5 g; 0.035 mol) in cumene (75 ml) are boiled under reflux under nitrogen for 10 hr. After removal of cumene, phosphite, and phosphate by distillation at reduced pressure, chromatography on alumina and elution with ether/light petroleum (b.p. 40–60°) affords 3-chloro-N-ethylphenothiazine (0.33 g; 14%; m.p. 115–117°) followed by 3-chlorophenothiazine; yield: 1.06 g (58%); m.p. and mixed m.p. 196°.

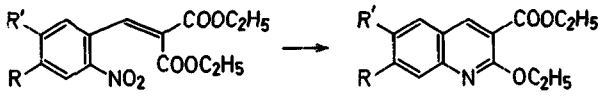
3-Methoxyphenothiazine (**62**, R = OCH_3) is similarly prepared in 85% yield.

2.2. Quinolines and Derivatives

Reductive cyclization with triethyl phosphite has been used as a route to oxazolo[5,4-b]quinolines (**63**; 45%)[35], benzo[c]naphthyridines (7%)[14], and quinolines (**64**; 61%)[34]:



63



64

R = R′ = H_3CO; R = H_3CO, R′ = H_5C_6—CH_2—O.

3. Seven-Membered Nitrogen-Containing Heterocycles

Reaction of diethyl methanephosphonite in an excess of diethylamine with 2-nitrobiphenyl or nitrobenzene affords 2-diethylamino-3-phenyl-3H-azepine (13%) or 2-diethylamino-3H-azepine (83%), respectively[9],

[31] A. Ur-Rahman and A. J. Boulton, Tetrahedron, **1966**, Suppl. 7, 49.

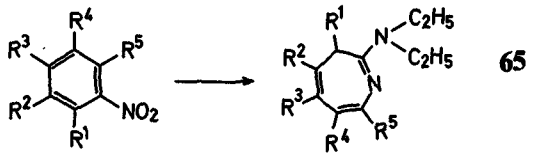
[32] A. J. Boulton, I. J. Fletcher, and A. R. Katritzky, Chem. Commun., **1968**, 62.

[33] T. Kametani, K. Ogasawara, and T. Yamanaka, J. Chem. Soc. [C], **1969**, 385.

[34] T. Kametani, K. Nyu, T. Yamanaka, H. Yagi, and K. Ogasawara, Tetrahedron Letters, **1969**, 1027.

[35] R. J. Sundberg, B. P. Das, and R. H. Smith, J. Amer. Chem. Soc., **91**, 658 (1969).

while photolysis of nitrobenzene, nitrotoluenes and nitromesitylene in triethyl phosphite with diethylamine also leads to 3H-azepines[35] (**65**):

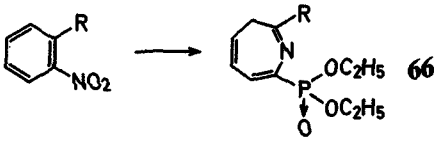


65

$(C_2H_5O)_2PCH_3$/thermal: R^1—R^5 = H; $R^1 = C_6H_5$, R^2—R^5 = H
$(C_2H_5O)_3P$/u.v.: $R^1 = R^3 = R^5 = CH_3$, $R^2 = R^4$ = H
$R^1 = CH_3$, R^2—R^5 = H;
$R^1 = R^2 = R^4 = R^5$ = H, $R^3 = CH_3$
R^1—R^5 = H.

2-Diethylamino-3H-azepine (**65**, R^1—R^5 = H): Nitrobenzene (2.5 g; 0.02 mol), diethyl methanephosphonite (18.5 g; 0.136 mol), and diethylamine (80 ml) are heated at the boiling point (55°) under nitrogen for 5 days. Low boiling materials are removed at < 100°/20 mm and the residue is chromographed on alumina. Elution with benzene/ether (9 + 1) gives an oil (2.73 g), exhibiting only one peak in g.l.c. Distillation affords 2-diethylamino-3H-azepine[36]; yield: 2.185 g (83%); b.p. 50—60°/0.05 mm; n_D^{25}: 1.5509.

Thermal reductions of simple nitrobenzenes in excess of triethyl phosphite also lead to phosphonylated 3H-azepines (**66**) in low (5—20%) yield[37]:



66

R = H, CH_3

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[36] as shown by the identity of its p.m.r. spectrum with that previously published by W. von E. DOERING and R. A. ODUM, Tetrahedron, **22**, 87 (1966).

[37] J. I. G. CADOGAN, R. K. MACKIE, and M. J. TODD, Chem. Commun., **1968**, 736; unpublished observations.